

### **REMARKS**

Claims 1, 2, 4, 5, 8, and 22 are pending in the application. Claim 4 stands withdrawn. Claims 1, 2, 5, 8, and 22 are currently under examination. In the present response claim 23 has been added. Support for this claim is found throughout the specification as filed, for example at paragraph [0213] on page 60. It is believed that no new matter has been introduced.

#### **35 U.S.C. § 112, first paragraph, enablement rejections**

Claims 1, 2, 5, 8, and 22 were rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph, for lack of enablement, allegedly because undue experimentation is needed to practice the invention.

According to the Office Action, it is alleged that "the specification, while being enabling for [a] method of identifying an increased likelihood of lupus nephritis in a mouse...it does not reasonably provide enablement for methods to diagnose lupus nephritis (LN) in a human." (See pages 2 and 3 of the Office Action.) In rejecting all of the pending claims, the Examiner has relied on several scientific publications to assert unpredictability in correlating mouse midkine gene expression in a murine lupus model with expression of the corresponding human gene in the human disease. The Office Action relies on Kotzin 1 (Cell, 1996, Vol. 85, pages 303-306), Kotzin 2 (J. Clin. Invest., 1997, Vol. 99, pages 557-558), Liu (Clin. Immun., 2004, Vol. 112, page 225), Morel (PLOS Biol., 2004, Vol. 2, p1061), and Enard (Science, 2002, Vol. 296, p. 340) to support these assertions.

Kotzin 1 is cited as allegedly teaching that environmental factors play a role in the manifestation of lupus and that because animal models are bred to have uniform symptoms, it is unclear if results from animal studies can be applicable to humans. Kotzin 2 is cited as allegedly teaching that lupus clinical manifestations and autoantibody production can be extremely diverse and variable." (See pages 5 and 6 of the Office Action.) However, Kotzin 1 teaches identification of autoantibodies and their presence in lupus in patients **and** mice. In fact, Kotzin 2 teaches that **NZB X NZW** mice are "one of the best-studied models of lupus nephritis." The specific mouse model utilized in the present application is NZB X NZW F1. Simply put, neither Kotzin 1 nor Kotzin 2 suggest that there is no correlation between midkine gene expression in mice and in humans.

Furthermore, Liu is cited as allegedly teaching that "their results show that murine models do not perfectly model corresponding human autoimmune diseases. (See page 7 of the Office Action.) However, Liu does not contemplate the specific mouse model utilized in the present application, i.e., NZB X NZW F1. The mouse model of the present invention demonstrates a correlation between midkine gene expression in the kidney and lupus. For at least this reason, the Liu reference is not applicable to assert unpredictability of the present claims. In addition, Applicants note that the Declaration submitted by Dr. O'Toole specifically

distinguishes the present results as involving a particular mouse model that is in fact a good model for lupus.

In addition, Morel is cited as teaching that "human autoimmune diseases (which include lupus) show extremely heterogeneous clinical presentation and that animal models only present a simplified version." (See page 8 of the Office Action.) Applicants respectfully submit that these observations are irrelevant to what is presently claimed, i.e., a method of identifying an increased likelihood of lupus nephritis associated with an elevated midkine **gene expression**. Morel does nothing to contradict or dispute a correlation between midkine gene expression in humans and in mice.

Furthermore, Enard is cited for the proposition that there are a large number of quantitative differences in gene expression between humans, chimpanzees, orangutans and rhesus macaques. (See page 8 of the Office Action.) As noted above, Dr. O'Toole has specifically stated the utility of the NZB X NZW F1 mouse model to the human disease. None of the examples in Enard dispute this fact. Enard merely compares gene expression patterns between different species. Furthermore, none of the examples in Enard analyze genes differentially expressed between healthy and lupus-diseased individuals of the same or of different species. And Enard does not analyze midkine gene expression in any of the organisms studied.

In addition to the Declaration of Dr. O'Toole, Applicants provide Kosugi et al. (Lab. Invest., 2007, Vol. 87, pp 903-913). A copy of this reference is attached as Exhibit I and is submitted also as a Supplemental IDS being filed concurrently with this response. Kosugi teaches that midkine gene expression in mice correlates with autoimmune disease in humans. (See page 906, first paragraph of the Results section.)

The Office Action also asserts that no evidence has been provided to support that the mTOR pathway correlates with lupus. Applicants hereby include Reddy et al. (Arthritis Res. Ther., 2008, 10:R127) copy of this reference is attached as Exhibit II and is submitted also as a Supplemental IDS being filed concurrently with this response. Applicants respectfully submit Reddy for the Examiner's attention for in their conclusions in the Abstract and in page 14, it teaches that their findings implicate the mTOR pathway as a critical contributor to human lupus.

In the Office Action of January 11, 2008, the Examiner stated that "the issue is not suitability of mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to humans." Applicants submit that Kosugi teaches that midkine gene expression in mice correlates with autoimmune disease in humans.

In summary, the Liu, Morel, and Enard references cited by the examiner do not relate to the NZB X NZW F1 mouse model and its correlation with a specific human disease. Similarly, none of the references are relevant to or even mention the midkine gene. Applicants provide here the Reddy reference as Exhibit II, which shows that the mTOR pathway is implicated in

mouse lupus nephritis models and in human lupus nephritis. Applicants also provide here the Kosugi reference as Exhibit I, which shows correlation of midkine gene expression with disease in mouse model and in humans.

In view of the foregoing, withdrawal of the rejection under 35 USC § 112, first paragraph, is respectfully requested.

#### CONCLUSION

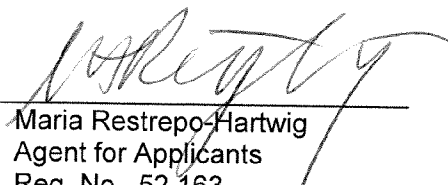
A petition for a three-month extension of time to file this response accompanies this paper.

In view of the above remarks Applicants respectfully submit that the Application is now in form of allowance. Allowance of the amended Application on the merits is respectfully requested.

If any outstanding issue remains, the Examiner is invited to contact the undersigned agent for a discussion of a mutually agreeable solution.

During the pendency of this application please treat any reply requiring a petition for extension of time for its timely submission as containing a request therefore for the appropriate length of time. Should the Commissioner determine that any fee(s) is due or that any credit for overpayment is required, the Commissioner is hereby authorized to charge any additional fee(s) and/or credit any overpayments to Deposit Account No. 01-1425.

Respectfully submitted,

  
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